Journal of Forensic and Legal Medicine 24 (2014) 12–14

Contents lists available at ScienceDirect

Journal of Forensic and Legal Medicine

journal homepage: www.elsevier.com/locate/jflm

Case report

Death due to fulminant neuroleptic malignant syndrome induced by low doses of haloperidol: A rare case

Donghua Zou, M.M. Assistant Professor [a], Yu Shao, M.M. Assistant Engineer [a], Zhiqiang Qin, B.M. Professor, Jianhua Zhang, M.M. Associate Professor *, Ningguo Liu, M.M. Professor, Zhengdong Li, M.M Assistant Engineer, Ping Huang, M.D., PhD. Associate Professor *, Yijiu Chen, M.M. Professor *

Shanghai Key Laboratory of Forensic Medicine, Institute of Forensic Science, Ministry of Justice, 1347 West Guangfu Road, Shanghai 200063, PR China

ARTICLE INFO

Article history:
Received 31 October 2013
Received in revised form
29 January 2014
Accepted 25 February 2014
Available online 6 March 2014

Keywords:
Neuroleptic malignant syndrome
Haloperidol
Low dose
Death
Forensic pathology

ABSTRACT

The paper reports on a rare case of fulminant neuroleptic malignant syndrome (NMS) with several risk factors, typical manifestation and rapid death induced by low doses of haloperidol. The pathological findings, pathogenesis, clinical manifestations, diagnostic criteria, risk factors and other features of NMS are discussed. The importance of forensic pathologists being aware of the possibility of NMS as the cause of death in people taking antipsychotic drugs is stressed.

1. Introduction

Neuroleptic malignant syndrome (NMS) is a rare but potentially severe idiosyncratic adverse reaction to antipsychotic medication,[1–3] and was first reported by Delay et al. in 1960.[3,4] It is characterized by the abrupt onset of fever, autonomic instability, extrapyramidal syndrome, and an altered mental state.[2,3,5] The pathogenesis of NMS includes drug-induced blockade of central dopamine receptors, central dopaminergic hyponeurotransmission and several other mechanisms.[4,6,7] Many risk factors that contribute to the onset of NMS have also been identified. The previous incidence of NMS ranged between 0.5 and 3% in the patients taking neuroleptic drugs, but a recent survey suggests an incidence of between 0.01 and 0.02%.[6,8] The syndrome has a considerable morbidity and high mortality.[1,3,6] Numerous typical and atypical antipsychotic drugs can result in NMS. The frequency of NMS with typical antipsychotic drugs is reported as being between 0.02 and 2.44%.[9] Haloperidol is one of the major inducers among the typical antipsychotic drugs, and the first report of NMS concerned exposure to haloperidol.[3] Among the patients treated with haloperidol, the incidence of NMS is between 0.5 and 1.0%,[5] but the reports of death in those with NMS following haloperidol treatment are uncommon.

In this paper, we report a rare case of death caused by fulminant NMS induced by low doses of haloperidol, and compare it with similar cases of NMS in the literature. Key pathological findings of the deceased are described, and the pathogenesis, clinical symptoms, diagnostic criteria and risk factors of NMS are discussed. Additionally, this paper stresses the importance of awareness of NMS following antipsychotic medication as a probable cause of death. Sometimes even low doses of neuroleptics such as haloperidol can be lethal.

2. Case report

A 33-year-old male was hospitalized and diagnosed with schizophrenia in 2009. He had intermittent episodes after discharge, and failed to follow his medication recommendations. He was recently admitted to hospital at 3 p.m. after maintaining mental disorders for 4 days due to being frightened at home. The abnormal behavior included insomnia, loud shouting, running

* Corresponding authors. Tel.: +86 21 52367986.
E-mail addresses: donghuazouifs@gmail.com (D. Zou), shaoyu1986@gmail.com (Y. Shao), qinzhiqiangifs@gmail.com (Z. Qin), zhangjianhuaifs@gmail.com (J. Zhang), liuningguoifs@gmail.com (N. Liu), zhengdongliifs@gmail.com (Z. Li), huangpingifs@gmail.com (P. Huang), yijiuchen@gmail.com (Y. Chen).
[a] D. Zou and Y. Shao contributed equally to this work.

http://dx.doi.org/10.1016/j.jflm.2014.02.011
1752-928X/

outside, and destruction of property. Physical examination at the hospital recorded a pulse rate of 120/min, respiration rate of 20/min, and blood pressure and temperature were unable to be obtained because of the patient's uncooperative behavior. White blood cell count was 16.2×10^9/L. Electrocardiogram (ECG) was also unable to be obtained. Neurological examination was normal. The patient displayed gibberish speech, loud shouting, struggling, emotional lability, and was uncooperative to inquiry, examination and treatment. The diagnosis was paranoid schizophrenia. The patient was restrained to a bed for his safety and received two intramuscular injections of haloperidol (5 mg) and scopolamine (0.3 mg) at 5 p.m. However, he continued to be noisy, became irritable and combative, and refused to eat and take medication, and was administered three intramuscular injections of haloperidol (5 mg), scopolamine (0.3 mg) and clonazepam (1 mg) at 8 p.m. The patient shouted intermittently and struggled throughout the night, unable to fall asleep.

At 6 a.m. on the second day, the patient suddenly became unconscious, displaying tachypnea and rigidity in all extremities with convulsions. His eyeballs turned up and showed anisocoria (5 mm on the left side and 4 mm on the right side) and were unresponsive to light. He displayed trismus, pale lips with foaming in the mouth, and coarse breathing and dry rales in both lungs were heard. His pulse rate was 158/min, his blood pressure fluctuated between 120/60 and 90/47 mm Hg, he had a temperature of 42 °C and a respiratory rate of 52/min. ECG showed tachycardia (153 bpm), ventricular extrasystole with Wolff-Parkinson-White syndrome. White blood cell count was 26.5×10^9/L. Blood urea nitrogen was 15.5 mmol/L, creatinine was 208 μmol/L, aspartate aminotransferase was 155.3 μ/L, alanine aminotransferase was 85.5 μ/L, sodium was 158 mmol/L, potassium was 3.3 mmol/L, and calcium was 1.04 mmol/L. Computer tomography of the brain was normal. Despite aggressive resuscitation, the patient died shortly thereafter.

During the autopsy, the body was measured to be 171 cm in height and 71 kg in weight. Several skin punctures due to medical procedures, and abrasions at both wrists and ankles due to protective restraints were found. Nothing else remarkable was observed. Histological investigation revealed cerebral and pulmonary edema together with generalized congestion of the internal organs. Myolysis of myocardium and chronic gastritis were also observed. The cause of death was determined as being NMS induced by haloperidol.

3. Discussion

Although the precise pathogenesis of NMS is still unclear, it is well recognized that the onset of NMS is attributable to the combination of a series of mechanisms. Neuroleptics are common blockers of dopamine receptors, which contain central and peripheral receptors. Blockade of dopamine receptors, together with dopaminergic hypotransmission and dopamine depletion in the hypothalamus, nigrostriatal system and mesocortical dopaminergic system are responsible for autonomic dysfunction, extrapyramidal symptoms and mental symptoms of NMS, respectively. Abnormalities in peripheral dopamine mechanisms could cause dysautonomia with increased excretion of epinephrine and norepinephrine, manifesting as a "hyper-adrenergic crisis". Interactions between imbalances in dopamine and various neurotransmitters, including GABA, Ach, norepinephrine and serotonin, for example, may also contribute to the development of NMS. Additionally, neuroleptics have a direct toxic effect on skeletal muscle by influencing intracellular second messenger systems and inducing abnormal calcium availability in muscle cells, thus triggering muscle rigidity, rhabdomyolysis and hyperthermia.[4,6,7,10] Typical symptoms of NMS consist of muscular rigidity, hyperthermia, autonomic dysfunction, altered consciousness, and elevated serum creatine phosphokinase levels.[2] Other manifestations include pallor and signs of congestion or infarction in the lungs.[5]

Several diagnostic criteria are used for NMS worldwide, including the DSM IV-TR criteria and the Levenson criteria,[2] which share quite similar content. In the present case, the patient demonstrated severe muscle rigidity with convulsions, fever (42 °C), tachycardia (153 bpm) with arrhythmia (Wolff–Parkinson–White syndrome), a sudden change in mental state (unconsciousness), labile blood pressure and leukocytosis (white blood cell count of 26.5×10^9/L) shortly after administration of haloperidol. These observations met the diagnostic criteria from both guidelines, and supported a diagnosis of NMS. While not affecting the final diagnosis, it was unfortunate that the patient's serum creatine phosphokinase level was not tested, possibly because NMS is far from being recognized in the general medical profession in some countries, such as China.

Besides the major symptoms, common complications of NMS include rhabdomyolysis, renal failure, sepsis, adult respiratory distress syndrome and pulmonary edema.[8] Associated laboratory features include impaired liver function tests, electrolyte disturbance, renal impairment, altered coagulation and ECG abnormalities.[3] In the present case, ECG abnormalities, impaired liver and renal function and electrolyte disturbance were indicated in the laboratory test results, accompanied with the onset of the symptoms. Additionally, pulmonary congestion and edema were confirmed by histological examination. These features correspond to a number of the complications and laboratory features of NMS.

Despite the positive diagnostic criteria, NMS is more a diagnosis of exclusion, so differential diagnoses are of prime importance.[6] Infections of the central nervous system, brain lesions, toxic or pharmacological side effects of drugs and several other causes should be excluded. In the present case, brain computed tomography and neurological examination were normal. No specific abnormalities of the central nervous system other than cerebral edema were detected during the autopsy and histological examination. The patient had received scopolamine and clonazepam as well as haloperidol. Nothing was found in the literature suggesting that scopolamine can cause symptoms such as those observed in the present case. There have been reports that rapid withdrawal of chronically administered clonazepam could induce catatonia[11]; however, this is inconsistent with the present case. Therefore, there is no evidence to suggest that some other cause was responsible, leaving NMS as the only viable option to explain all the symptoms.

Important risk factors of NMS include rapid changes in drug dosages, hyponatremia, pre-existing medical and neurological disorders, recent use of restraints, iron deficiency, and certain physiological states of the patient at the time of drug exposure, like exhaustion or dehydration.[3,5,12] Both males and females of all ages are susceptible to NMS, with the syndrome being most common in young adult males. Studies suggest that genetic factors may also be involved.[4] In the present case, the patient had suffered from schizophrenia for the past few years. After admission, he struggled with shouts before restrained to a bed. He remained in a continuously intense excitatory state, he refused to eat, and his rapid breathing would lead to dehydration and exhaustion, leaving him in a poor physical and mental state when exposed to neuroleptics. Unfortunately, these factors resulted in the young adult male patient being more susceptible to NMS.

The majority of NMS cases commences within 2 weeks of the initiation or change in dose of drug treatment. Occasionally, there may be a fulminant onset within hours of drug administration. About 16% of NMS cases develop within 24 h after initiation of drug treatment.[2,3,6,9] In the present case, the patient had an episode

within 12 h of administration of haloperidol, followed by a critical condition period and a rapid death thereafter, which can be considered as a fulminant type of NMS.

NMS is associated with many typical and atypical antipsychotic drugs, and haloperidol is one of the classic inducers among the typical types. In the present case, the patient received 10 mg of haloperidol (5 mg per injection), which is a relatively low dose when compared with doses in other NMS cases induced by haloperidol in the literature.[1,5,8] But NMS is an idiosyncratic disorder, and the onset of the syndrome is not related to the duration of exposure to neuroleptics or to toxic doses.[4] There is also a case in the literature that reports NMS induced by a single intramuscular injection of haloperidol (5 mg).[13] It is therefore possible and plausible that such a low dose of haloperidol could trigger NMS in the present case.

Regarding the cause of death, besides indications of NMS, skin lesions, myolysis of myocardium and chronic gastritis were observed during autopsy. The skin injuries were slight and superficial and not located in vital parts of the body. Myolysis of myocardium was considered to be the consequence of myocardial ischemia and hypoxia due to an internal environment disorder caused by NMS. Chronic gastritis had no direct association with the rapid death, but the pre-existing impaired digestive function may have accelerated the dying process. No other abnormalities were detected during either antemortem or postmortem examinations. Therefore, the cause of death was determined as NMS.

In conclusion, this paper reports a rare death due to fulminant NMS induced by low doses of haloperidol. The patient had several risk factors of NMS, and had suffered an abrupt onset, followed by a critical condition period and rapid death. The clinical manifestations and laboratory test results corresponded to the diagnostic criteria of NMS.

Because of the low incidence but high severity and mortality of NMS, this case report serves as a reminder to forensic pathologists to be aware of the possibility of NMS in cases of death in which people take antipsychotic drugs. Similar clinical manifestations should be carefully differentiated from seizure attacks, infections and other possibilities. It ought to be noted that even low doses of antipsychotic drugs such as haloperidol can trigger NMS.

Ethical approval

None.

Funding

Financial support for this work were provided by Key Projects in the National Science & Technology Pillar Program during the Twelfth Five-Year Plan Period, No. 2012BAK16B02, and by Programs of the Science and Technology Commission of Shanghai Municipality, No. 13DZ2271500.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Chopra MP, Prakash SS, Raguram R. The neuroleptic malignant syndrome: an Indian experience. *Compr Psychiatry* 1999;**40**:19–23.
2. Musshoff F, Doberentz E, Madea B. Lethal neuroleptic malignant syndrome due to amisulpride. *Forensic Sci Med Pat* 2013;**9**:218–20.
3. Trollor JN, Chen X, Sachdev PS. Neuroleptic malignant syndrome associated with atypical antipsychotic drugs. *CNS Drugs* 2009;**23**:477–92.
4. Adnet P, Lestavel P, Krivosic-Horber R. Neuroleptic malignant syndrome. *Br J Anaesth* 2000;**85**:129–35.
5. Samar RK, Kaushik SK, Garg AR. Malignant neuroleptic syndrome due to haloperidol. (A case report). *J Postgrad Med* 1983;**29**:56–60.
6. Strawn JR, Keck Jr PE, Caroff SN. Neuroleptic malignant syndrome. *Am J Psychiatry* 2007;**164**:870–6.
7. Mann SC, Caroff SN, Lazarus A. Pathogenesis of neuroleptic malignant syndrome. *Psychiatr Ann* 1991;**21**:175–80.
8. Maheshwari M, Shankaragouda BH, Savadkar A, Vaishnav S. Haloperidol induced neurolept malignant syndrome complicated by right ventricular myocardial infarction. *Indian Med Gaz*; 2013:79–80.
9. Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant syndrome and atypical antipsychotic drugs. *J Clin Psychiatry* 2004;**65**:464–70.
10. Mizuno Y, Takubo H, Mizuta E, Kuno S. Malignant syndrome in Parkinson's disease: concept and review of the literature. *Parkinsonism Relat Disord* 2003;**9**:3–9.
11. Brown M, Freeman S. Clonazepam withdrawal-induced catatonia. *Psychosomatics* 2009;**50**:289–92.
12. Steele D, Keltner NL, Mcguiness TM. Are neuroleptic malignant syndrome and serotonin syndrome the same syndrome? *Perspect Psychiatr Care* 2011;**47**:58–62.
13. Konikoff F, Kuritzky A, Jerushalmi Y, Theodor E. Neuroleptic malignant syndrome induced by a single injection of haloperidol. *Brit Med J* 1984;**289**:1228–9.